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# Immunotherapy for Prostate Cancer: False Promises or True Hope?

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## Abstract

Prostate cancer is the most commonly diagnosed cancer, and the second leading cause of cancer-related death, for men in the United States. Despite the approval of several new agents for advanced disease, each of these has prolonged survival by only a few months. Consequently new therapies are sorely needed. For other cancer types, immunotherapy has demonstrated dramatic and durable treatment responses, causing many to hope that immunotherapies might provide an ideal treatment approach for advanced prostate cancer. However, apart from sipuleucel-T, prostate cancer has been conspicuously absent from the list of malignancies for which immunotherapies have received recent FDA approval. This has left some wondering if immunotherapy will "work" for this disease. In this review we describe current immunotherapy developments, including approaches to engage tumor-targeting T cells, disrupt immune regulation, and alter the immunosuppressive tumor microenvironment. We then describe the recent application of these approaches to the treatment of prostate cancer. Given the FDA approval of one agent, and the fact that several others are in advanced stages of clinical testing, we believe that immunotherapies offer real hope to improve patient outcomes for prostate cancer, especially as investigators begin to explore rational combinations of immunotherapies and combine these therapies with other conventional therapies.

## Graphical abstract

**Condensed Abstract:** In this review we highlight the history of immunotherapeutic development for prostate cancer and many of the strategies currently being explored. We conclude that immunotherapies have promise for improving clinical outcomes, and that the greatest benefits will come as immunotherapy approaches begin to be rationally combined with other therapies.

### Keywords

Prostate cancer; immunotherapy

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## Goals of Cancer Immunotherapy

The relationship between the human immune system and the development of cancer has been both well-studied, and hotly-debated, for over a century. From the foundational work by Paul Ehlrich in the early 1900s[1], to Burnet and Thomas's "cancer immunosurveillance" hypothesis of the 1950s[2], to the most recently revised theory of "cancer immunoediting" by Schreiber and colleagues[3], many have proposed a role for the immune system in controlling the development of cancer. However, until recently there was little clinical evidence demonstrating consistent anti-tumor responses following immune-based therapies. Many recent clinical trials, however, have demonstrated that the immune system can have potent anti-tumor activity in many cancer types. With recent trials demonstrating that CTLA-4 and PD-1 blockade can increase survival for patients with metastatic melanoma and other diseases[4,7], to the current phenomenal results observed with CAR T cells for B-cell malignancies[5], there is now no doubt that the immune system is a powerful anti-cancer tool. In fact, the designation of cancer immunotherapy as the 2013 scientific breakthrough of the year by *Science* effectively marked that cancer immunotherapy was no longer a theoretical possibility but a practical reality[6]. Given the recent momentum and interest in this field, many now believe that cancer immunotherapy will be a cornerstone of treatment for most cancers.

There is great diversity among the many cancer immunotherapies currently under investigation, but they can be loosely classified into three distinct categories based on their end goal: eliciting tumor-targeting cytolytic lymphocytes, disrupting immune regulation, and altering the tumor microenvironment (Figure 1). The first class of agents are designed to supply or augment the frequency of T cells in a patient specific for one or more tumor-associated antigens, or other non-antigen-specific anti-tumor effector cell populations such as NK cells. This can be carried out both *in vivo*, through the delivery of vaccines and cytokines, or *ex vivo*, through collecting, modifying/expanding and reinfusing these cells. Other cancer immunotherapies work by repressing the tumor's ability to circumvent anti-tumor immunity. Because cancers derive from a patient's own cells, they can maintain and exploit normal autoimmune defense mechanisms. Successfully disrupting these inhibitory pathways co-opted by cancers have proven to be remarkably effective in the case of checkpoint inhibitors. The last class of cancer immunotherapies work by altering the tumor microenvironment, turning what is often an unfavorable environment for productive anti-tumor immunity into one that is more favorable, typically by changing the types of cells that might be present at the tumor site or by disrupting the tumor vasculature, making the tumor environment more amenable to immune cell infiltration and destruction.

Prostate cancer is one malignancy for which there has been much exploration of immunotherapeutic agents. Due to its typically slow progression, abundance of tissue-specific target antigens, a reliable serum marker to assess clinical responses, and the non-essential nature of the target tissue (reducing concerns about autoimmune destruction of normal prostate cells), prostate cancer is in many ways an ideal malignancy for evaluating new immunotherapy treatments. And because prostate cancer remains the most commonly diagnosed cancer and second leading cause of cancer-related death for men in the United States, new therapies are sorely needed[7]. However, apart from sipuleucel-T, prostate cancer

has been conspicuously absent from the list of malignancies for which new immunotherapies have been recently FDA approved, leaving many wondering if immunotherapy can provide any real hope for improving patient outcomes. In this review we highlight the history of immunotherapeutic development for prostate cancer and many of the strategies currently being explored. We conclude that immunotherapies have real promise for improving clinical outcomes, and that the greatest benefits are yet to come as immunotherapy approaches begin to be rationally combined with other therapies.

## History of Immunotherapy for Prostate Cancer

### Cytokines

The first class of immunotherapies are agents designed to increase the frequency or activity of T cells specific for one or more targets overexpressed by tumors (tumor-associated antigens, TAAs). Some of these first attempts were through the delivery of cytokines, as prior work had shown that the delivery of IL-2 could successfully expand tumor-reactive T-cell populations and elicit anti-tumor immune responses in patients with melanoma or renal cell cancer[8,9]. A phase I trial explored the intratumoral delivery of IL-2 in prostate cancer patients with either locally advanced or recurrent disease following prostatectomy[10]. Although the treatment was well tolerated and they observed increased T-cell infiltration into tumors, only modest changes in prostate-specific antigen (PSA) levels were observed. Another group examined the safety and efficacy of an IL-2 immunocytokine, EMD 273066 (huKS-IL2), a human EpCAM-targeting antibody fused with IL-2. This treatment was also well tolerated, but also showed little signs of anti-tumor activity[11]. Another group examined the efficacy of subcutaneous IL-2 in combination with interferon-alpha (IFNα) in patients with metastatic prostate cancer and again observed no improvements in regards to PSA levels or survival[12]. Together, all of these trials demonstrated that, although well tolerated, IL-2 cytokine therapy (in various formats) was not able to elicit a meaningful anti-tumor immune response as a monotherapy, and thus its evaluation in prostate cancer therapy has essentially been discontinued.

Similarly, phase I trials treating patients with either intratumoral IFNα, or with intratumoral tumor necrosis factor-alpha (TNFα) along with systemic IFNα2b, demonstrated that these treatments again were well tolerated but exhibited little clinical activity[13,14]. Conversely, clinical trials examining systemic treatment with GM-CSF as a monotherapy have shown some signs of efficacy (Table 1-line 1, Table-L1). In a Phase II trial examining treatment of patients with CRPC with GM-CSF in combination with thalidomide, nearly all patients experienced a transient decrease in PSA levels, and a trial employing similar treatment in patients with non-castrate resistant prostate cancer also demonstrated a marked decrease in PSA levels in nearly 90% of patients[15,16]. Another trial also demonstrated that long-term treatment of GM-CSF in patients with recurrent disease was well tolerated and that a substantial fraction of patients experienced long-term disease control[17]. Taken together, these findings suggest that, while well tolerated, the systemic or intratumoral delivery of cytokines seems able to elicit only marginal anti-tumor responses in prostate cancer patients when given as single agents. There may be promise for GM-CSF as a monotherapy, but there has been more interest in the combination of cytokines with other immunotherapies.

## Vaccines

As a more specific means of amplifying tumor-specific T cells, others have explored the use of anti-tumor vaccines. This approach is especially relevant to prostate cancer given the abundance of target proteins that are nearly exclusively expressed in prostate tissue, dampening concerns about off-target side effects. Previous data have also shown that T cells (and antibodies) specific for several of these prostate-specific targets can exist in the peripheral blood of prostate cancer patients, suggesting that vaccines may be useful to augment prostate-specific T-cell populations[18,19].

An early vaccine to enter clinical testing for prostate cancer was GVAX-PCa, a mixture of irradiated PC-3 and LNCaP cell lines engineered to overexpress GM-CSF, with the goal of eliciting T cells specific for one or more TAAs[20]. Phase I/II trials indicated that the treatment was well tolerated and induced antibody responses to various proteins in the cell lysates, suggesting the vaccine was eliciting antigen-specific immune responses[20,21]. Higher doses of treatment appeared to be associated with prolonged survival compared to lower doses. However, two independent phase III trials were closed prematurely due to lack of superior clinical efficacy compared to chemotherapy in one trial, and an increase in patient mortality observed in the other trial (hazard ratio, 1.03 [95% C.I. 0.83-1.28], P=0.78)[22].

Other groups have explored the use of vaccines encoding one or more specific prostate cancer TAA, such as sipuleucel-T (Provenge®, Dendreon Corporation), an autologous antigen-presenting cell (APC) vaccine in which a patient's peripheral blood APC are isolated, pulsed with recombinant GM-CSF fused to the TAA prostatic acid phosphatase (PAP), and then re-infused 72 hours later (Table-L3). In a phase III trial, patients receiving sipuleucel-T had a greater median overall survival (25.8 months) versus patients receiving placebo (21.7 months), leading to its FDA approval in 2010 (hazard ratio, 0.78 [95% C.I. 0.61-0.98]; P=0.03)[23]. This made sipuleucel-T the first FDA-approved vaccine for the treatment of any cancer, and provided the first solid evidence that vaccines could provide a real benefit in disease outcome for prostate cancer patients.

Many other groups have explored different vaccine platforms and target antigens. A highly anticipated vaccine currently under development is PSA-TRICOM (Prostvac®, Bavarian Nordic), a vaccinia and fowlpox viral vector approach encoding PSA (Table-L4)[24]. Early phase trials demonstrated the tolerability and immunological activity of PSA-TRICOM and two independent phase II studies reported an increase in overall survival for patients receiving PSA-TRICOM compared to placebo or historical controls[25,26]. A phase III approval trial is currently underway in patients with mCRPC (NCT01322490).

Other groups have explored different vaccine constructs targeting these or similar antigens. Both PAP and PSA have been targeted using DNA-based vaccination, with a DNA vaccine encoding PAP currently being evaluated in a randomized phase II trial (Table-L7, NCT01341652)[27,28]. These and other trials have demonstrated the tolerability of DNA immunization and their ability to elicit antigen-specific T cells, using a simpler platform than those of either Prostvac or sipuleucel-T. Still others are exploring the use of *Listeria monocytogenes* as a potentially more potent means of antigen delivery, particularly given evidence of clinical activity of listeria-based vaccines for pancreatic cancer[29]. Specifically,

recombinant listeria encoding PSA, PAP, and other TAAs are under investigation for treating advanced prostate cancer (Table-L15,16; NCT02625857, NCT02325557). While the approval of sipuleucel-T suggests that tumor vaccines have a place in the treatment of prostate cancer, it is not currently known if one vaccine approach is superior to another in terms of anti-tumor effects. Trials comparing different vaccine strategies, as well as trials combining vaccines with other immune-modulating agents, are eagerly anticipated.

## CAR T cells and Bispecific Antibodies

As a more direct means of providing tumor-reactive T cells, others have explored the use of adoptive cell therapy using *ex vivo* expansion of tumor-reactive T cells, or T cells engineered to be specific for a particular TAA by modifying their T cell receptors (TCRs). Recent studies have demonstrated dramatic anti-tumor activity using T cells engineered to express a chimeric antigen receptor (CAR) that permits recognition of a cell-surface protein using an antibody-recognition domain fused to the TCR signaling domain[30]. Specifically, CAR T cells targeting CD19 have led to complete responses in some B cell malignancies, prompting exploration of CAR T cells for other malignancies[31]. The availability of tissue-specific membrane proteins has limited development of this approach for many solid tumors. However, for prostate cancer some groups are exploring targeting prostate-specific membrane antigen (PSMA) using CAR T cell approaches[32,33]. A phase I dose-escalation trial evaluating PSMA-specific CAR T cells is currently underway (Table-L29, NCT01140373).

Another means to increase the reactivity of T cells to tumor cells is through the use of bispecific antibodies (e.g. BiTEs®, Amgen). These consist of the binding domain of two antibodies, one specific for the T cell, such as CD3, and the other specific for a desired membrane-associated TAA, fused together[34]. These dual antibodies then force the physical encounter of tumor cells by T cells. Work in preclinical models has demonstrated that a CD3xPSMA bispecific antibody was able to efficiently direct T cells toward tumors and could initiate cytolytic responses[35]. The one major benefit of these over CAR T cells is that they are effectively an “off-the-shelf” product, as they do not require the collection and reinfusion of a patient’s autologous T cells. This could allow bispecific antibodies to be a more cost-effective, and therefore hopefully more widely accessible, treatment option. However, like CAR T cells, they carry the same concerns regarding off-target toxicity for targets that are not completely tumor-specific, including PSMA. These concerns will be more thoroughly understood following the completion of two currently underway phase I trials examining the safety and efficacy of CD3xPSMA or CD3xEpCAM bispecific antibodies in patients with CRPC (Table-L30-32; NCT01723475, NCT00635596).

## T-Cell Checkpoint Blockade

The second class of immunotherapies works by disrupting the tumor cells’ ability to repress anti-tumor immunity. Because cancer cells derive from a patient’s own cells, they retain and can exploit defense mechanisms that cells have developed to avoid autoimmune destruction. These mechanisms include interference with molecules on T cells that regulate their expansion and function, known as immune checkpoints. Early work in this field identified the first of these T-cell checkpoint molecules, CTLA-4, as a major inhibitor of cytolytic anti-

tumor T-cell responses[36]. Preclinical and subsequent clinical work demonstrated that antibodies blocking CTLA-4 (preventing its ligation by CD80/CD86) could prevent this T-cell repression from occurring, ultimately leading to the approval of ipilimumab (Yervoy®, Bristol-Myers Squibb) for the treatment of metastatic melanoma[4]. Subsequent work has identified many other checkpoint molecules similar, but not redundant, to CTLA-4 including most notably PD-1, TIM-3, and LAG-3. Ligation of these molecules by tumor-expressed molecules also leads to decrease in T-cell effector function. Antibodies blocking PD-1 have recently received FDA approval for the treatment of melanoma, non-small cell lung cancer, and renal cell cancer[37–39].

In the case of prostate cancer, an early phase I/II trial treating mCRPC patients with ipilimumab (Table-L34) as either a monotherapy or in combination with radiotherapy demonstrated that some patients receiving the combination had a decrease in PSA levels and stable disease (with one complete response)[40]. This led to a randomized phase III trial in patients with mCRPC receiving either ipilimumab or placebo after radiotherapy[41]. This trial, although demonstrating a difference in progression-free survival between the two groups, did not demonstrate a significant difference in overall survival (ipilimumab: 11.2 months; placebo: 10.0 months; hazard ratio, 0.85 [95% C.I. 0.72-1.00]; P=0.053).

More recently, groups have also examined the treatment of prostate cancer with PD-1 blockade (Table-L33,36). Two independent phase I trials conducted using PD-1 blockade in patients with many types of solid tumors included those with mCRPC[42,43]. No objective responses were observed in the 25 mCRPC patients who were treated in both of these trials. A phase II trial is currently underway more thoroughly examining the anti-tumor efficacy of PD-1 blockade in patients with mCRPC (NCT02312557). However, results to date examining either CTLA-4 or PD-1 blockade alone have suggested little role for these treatments as monotherapy for prostate cancer. It remains to be seen if other checkpoint inhibitors will be more effective in prostate cancer, or if CTLA-4 or PD-1 blockade will be more effective when used in combination, as is currently underway (NCT01420965).

## Microenvironment Disruptors

The last class of immunotherapy agents is those designed to disrupt or otherwise modify the immunosuppressive tumor microenvironment, making it more amenable to a cytolytic immune response. Many tumors are infiltrated by regulatory T cells and/or myeloid-derived suppressor cells (MDSCs), which have been shown to repress anti-tumor immune responses by either direct cell-cell interactions or secretion of inhibitory molecules such as IL-10, nitric oxide or indoleamine 2,3-dioxygenase (IDO). Tumors are also known to have altered or disorganized vasculature, often not expressing the appropriate ligands necessary for immune cell trafficking. Agents designed to disrupt the tumor vasculature and/or deplete tumor-infiltrating regulatory cells have been shown to have antitumor activity in many cancer types. Among several of the approved agents targeting the vascular endothelial growth factor receptors, one agent, sunitinib (Sutent®, Pfizer), has been shown to inhibit tumor angiogenesis and also deplete MDSCs from tumors (Table-L38)[44]. Several independent phase II trials examining sunitinib as monotherapy for patients with mCRPC demonstrated signs of efficacy, as marked by PSA declines and objective responses, leading

to a randomized, placebo-controlled phase III trial of sunitinib in patients with mCRPC[45,46]. This trial revealed that sunitinib increased progression-free survival, but did not impact overall survival compared to placebo (sunitinib: 13.1 months; placebo: 11.8 months; hazard ratio, 0.914 [95% C.I. 0.762-1.097]; P=0.17)[47]. Combinations of VEGFR-targeting agents with chemotherapy have similarly not demonstrated significant benefit in prostate cancer[48]. Nonetheless, there remains interest in combination treatment using these agents specifically with immune-targeted therapies. In addition, chemotherapy and radiation therapy, agents already used in the management of prostate cancer that can disrupt tumor vasculature, are also being explored in combination with immune-targeted therapies (NCT02649855).

Another immunotherapy shown to impede the recruitment of MDSCs and to have antiangiogenic activity, tasquinimod[49,50], has been evaluated in patients with recurrent prostate cancer. Early trials demonstrated it was well tolerated and led to a significant increase in progression-free survival and overall disease control (stable disease and objective responses) compared to placebo[51]. An international double-blind, placebo-controlled phase III trial in men with mCRPC, however, showed no significant increase in overall survival (hazard ratio, 1.097 [95% C.I. 0.938-1.282])[52]. Despite this, there remains interest in the use of tasquinimod in combination with other immunotherapies.

## Likelihood of Success

Of all immunotherapy approaches currently being pursued for prostate cancer, the most successful to date have been vaccines. Vaccines have been shown to be well tolerated, able to elicit both antibodies and cytolytic T cells specific for TAAs, and to prolong overall survival in prostate cancer patients. This is intriguing given the relatively disappointing results vaccines have shown for most other malignancies. Prostate cancer is currently the only malignancy for which a vaccine is FDA approved and for which another vaccine is currently in phase III approval testing. In contrast, T-cell checkpoint inhibitors to date have shown less activity in the treatment of prostate cancer, at least as monotherapies, relative to other solid tumors. These findings suggest there could be differences in the immunogenicity of prostate tumors relative to other cancer types. In fact it has been suggested that prostate tumors have a lower frequency of infiltrating immune cells compared with many other solid tumor types[53]. Consequently, it is conceivable that anti-tumor vaccines have demonstrated activity for this disease simply by increasing the number of tumor-specific infiltrating T cells, compared with other tumors in which there may already be abundant T-cell infiltration.

Even with the potential that vaccines have shown in treating prostate cancer patients, the benefit shown to date by sipuleucel-T is fairly modest in terms of overall survival. This treatment has struggled to gain widespread use, possibly due to high cost, or median survival benefit of only 4 months, or because it is a first-in-class drug with which clinicians are less familiar. This has prompted many to study other simpler vaccines, study vaccines in combination with other therapies, or study vaccines at different stages of disease. In modeling the treatment effect of PSA-TRICOM, Madan and colleagues have suggested that vaccines may work to slow disease progression. In this case, vaccines may have their greatest effect in earlier stages of disease or combined with therapies to reduce tumor burden[54]. Numerous trials are currently underway examining the efficacy of either

sipuleucel-T or PSA-TRICOM at delaying disease progression in patients with earlier stages of disease (Table-L4, NCT02326805, NCT01431391, NCT00779402).

As described above, the T-cell checkpoint inhibitors that have been investigated to date, while active as monotherapies for many solid tumors, have been relatively disappointing as treatments for prostate cancer. However, as checkpoint inhibitors work by enhancing the activity of tumor-reactive T cells otherwise repressed by the tumor, and as prostate cancer may have fewer of these infiltrating T cells, these findings are perhaps not surprising. Other groups have also shown that the malignancies for which checkpoint blockade tends to be most effective are those with the highest mutational loads, presumably because T cells that can recognize these aberrantly expressed high-affinity neo-epitopes have high levels of checkpoint receptors and are otherwise dysfunctional in the absence of checkpoint blockade[55]. Prostate tumors are known to have a lower mutational burden than many other tumor types, decreasing the frequency with which T cells might recognize a mutated neo-epitope antigen leading to tumor-infiltrating T cells[56]. These findings suggest that checkpoint blockade may be more effective for prostate cancer when combined with vaccines or other therapies that augment tumor-specific T cells. In fact, it has recently been demonstrated that treating patients with either sipuleucel-T or another prostate cancer vaccine led to the upregulation of the checkpoint ligand PD-L1 on the surface of tumor cells, and that antigen-specific immune responses could be enhanced when combined with PD-1 blockade[57]. Groups have also demonstrated in pre-clinical models that anti-tumor vaccine efficacy could be enhanced when combined with checkpoint blockade[58,59]. Many groups have therefore begun exploring the combination of anti-tumor vaccines with checkpoint blockade in clinical trials. One recently reported trial which examined GVAX-PCa combined with ipilimumab for patients with mCRPC found that the combination treatment was generally well tolerated and was able to elicit anti-tumor responses (as measured by PSA decline) in some patients[60]. Another trial combining PSA-TRICOM with ipilimumab had similar findings[61]. Many other clinical trials examining these combination approaches are currently underway (Table-L16, NCT02499835, NCT02325557, NCT02506114, NCT01804465).

Radiation therapy, chemotherapy, and androgen deprivation therapy are all standard treatments in the management of prostate cancer, and all also have immune modulating activities. All three treatments can cause tumor cell death, potentially leading to release of prostate tumor antigens. Androgen deprivation has distinct immune-modulating activities by leading to thymic release of naïve T cells and can specifically lead to T-cell infiltration of prostate tumors[62]. Radiation therapy and chemotherapy can also disrupt tumor vasculature, raising the possibility that these treatments may make the tumor microenvironment more amenable to the development of an immune response. For all of these reasons, there is a strong rationale for combining these standard therapies with immunotherapies. On the other hand, both chemotherapy and radiation therapy can have immunosuppressive effects, underscoring the importance of careful planning and trials needed to determine optimal treatment strategies for patients with various stages of disease.

## A Model for Success – Rational Combination Approaches

As recurrent prostate cancer is one of the leading causes of cancer-related death in the United States, there is a great need for the development of novel therapies. Within the last five years several targeted agents have been approved for prostate cancer, but each has demonstrated a median prolongation of survival of only a few months. The field of cancer immunotherapy continues to grow and several agents have demonstrated dramatic successful anti-tumor activity for some diseases, including responses that continue after treatment has been discontinued. To date, while different immunotherapy approaches have been investigated for prostate cancer, including vaccines, checkpoint inhibitors, and tumor microenvironment disrupting agents, the results from each of these treatments as monotherapies has been more modest. Notwithstanding, clinical signals have been observed with cytokine-based therapies, CTLA-4 blockade, and with treatments that affect the immune regulatory populations within the tumor microenvironment. And prostate cancer is a disease for which vaccines have demonstrated clinical activity as single agents, with sipuleucel-T being the first vaccine to receive FDA approval for the treatment of any malignancy. These findings and observations suggest that optimal treatment effect may be observed when immunotherapy agents will be used in combination, and specifically combining treatments aimed at increasing the frequency tumor-reactive T cells (e.g. by vaccination, androgen deprivation, radiation therapy, or chemotherapy) with agents to increase their effectiveness (e.g., cytokines, checkpoint blockade, or regulatory cell function blockade). Many clinical trials evaluating these approaches are currently underway, and we believe that the rational combination of immunotherapies with other standard cancer therapies will lead to markedly improved treatments for patients with prostate cancer over the next decade.

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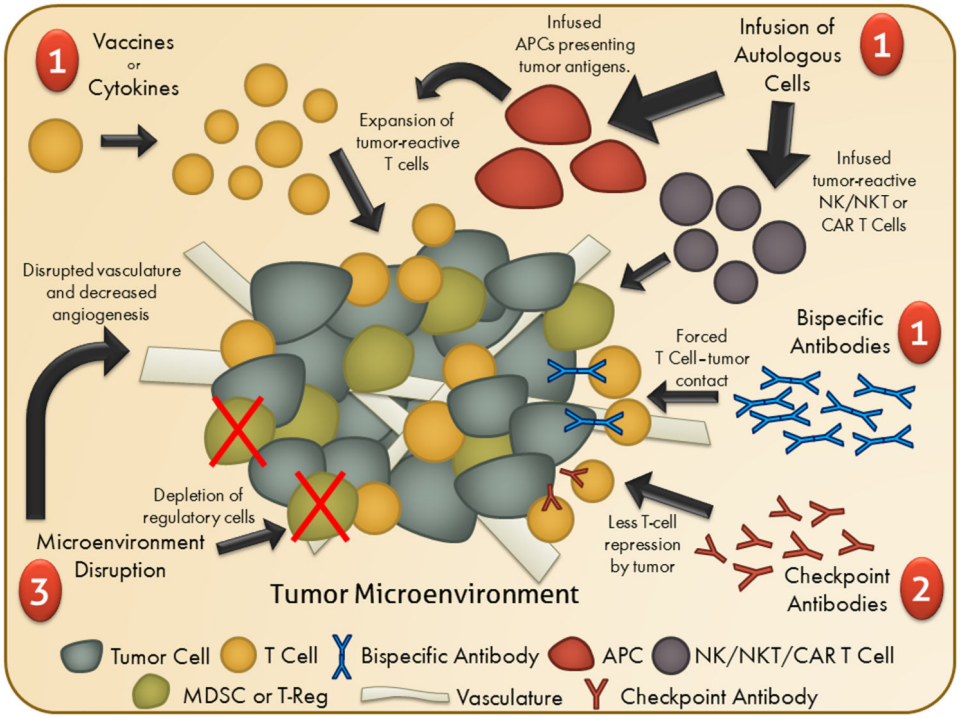


**Figure 1. Schematic of Immunotherapy Classes**

Shown is a schematic of the classes of immunotherapy approaches being investigated for the treatment of prostate cancer including (1) approaches to increase tumor-targeting cytolytic lymphocytes (e.g. vaccines, cytokines, adoptive transfer of cytolytic anti-tumor cells, or bispecific antibodies); (2) approaches to disrupt immune regulation; and (3) approaches to disrupt the immunosuppressive tumor microenvironment.

**Table 1**

Summary of Immunotherapies Approved or in Clinical Testing for Prostate Cancer

| | # | Drug Name | Description | Current Phase | Results | Ongoing Trials | References |
|---|---|---|---|---|---|---|---|
| Cytokines | 1 | GM-CSF | Systemic recombinant GM-CSF (sometimes with thalidomide) | II | Δ[a] in PSA levels<br>No SAE[a,b]<br>Some SD[a] | NCT00678054 (and many combinations) | 15 – 17 |
| | 2 | F16IL2 | Immunocytokine, antibody specific for tenascin-C fused with recombinant IL-2 | I/II | N/A | NCT01134250 | |
| Vaccines | 3 | Sipuleucel-T | Autologous APCs loaded with PAP-GM-CSF fusion protein | FDA Approved | IR[a] elicited<br>Few SAE<br>Δ in OS[a] | Many Combinations | 23,63,64 |
| | 4 | PSA-TRICOM | Vaccina/Fowlpox virus-based vaccine encoding PSA | III | IR elicited<br>Few SAE<br>Δ in OS | NCT01322490<br>NCT02326805<br>(and many combinations) | 24 – 26 |
| | 5 | DCVAC | Autologous APCs loaded with LNCaP tumor cell lysate | III | IR elicited<br>No SAE<br>Δ in OS | NCT02111577 | 65 |
| | 6 | Ad/PSA | Adenovirus-based vaccine encoding PSA | II | IR elicited<br>No SAE<br>Δ in PSA DT[a] | NCT00583752<br>NCT00583024 | 66 |
| | 7 | pTVG-hPAP | DNA vaccine encoding PAP | II | IR elicited<br>No SAE<br>Δ in PSA DT | NCT01341652<br>(and combinations) | 27 |
| | 8 | Natural DCs | Autologous dendritic cells loaded with NY-ESO-1 and MUC1 peptides | II | N/A | NCT02692976 | |
| | 9 | ME TARP | Autologous dendritic cells loaded with TARP peptides | II | N/A | NCT02362451<br>NCT02362464 | |
| | 10 | GX301 | Synthetic multi-peptide vaccine targeting telomerase | II | N/A | NCT02293707 | |
| | 11 | Tecemotide | Synthetic lipopeptide vaccine targeting MUC-1 | II | N/A | NCT01496131 | |
| | 12 | UV1/hTERT2012P | Synthetic peptide vaccine | II | N/A | NCT01784913 | |
| | 13 | RNActive | mRNA vaccine targeting multiple antigens | II | N/A | NCT02140138 | |
| | 14 | INO-5150 | DNA vaccine encoding PSA and PSMA | I | N/A | NCT02514213 | |
| | 15 | JNJ-64041809 | Live attenuated double deleted (LADD) *Listeria monocytogenes* encoding PAP, SSX2, and | I | N/A | NCT02625857 | |

| | # | Drug Name | Description | Current Phase | Results | Ongoing Trials | References |
|---|---|---|---|---|---|---|---|
| | | | NKX3.1 | | | | |
| | 16 | ADXS31-142 | Live attenuated *Listeria monocytogenes* encoding PSA | I | N/A | NCT02325557 | |
| | 17 | alpha-DC1 | Autologous dendritic cells loaded with allogenic prostate cell lines | I | N/A | NCT00970203 | |
| | 18 | BPX-201 | Autologous dendritic cells with DeCIDe activation technology | I | N/A | NCT01823978 | |
| | 19 | pTVG-AR | DNA vaccine encoding AR LBD | I | N/A | NCT02411786 | |
| | 20 | VANCE | ChAdOx1 and MVA virus-based vaccine encoding 5T4 | I | N/A | NCT02390063 | |
| | 21 | ProscaVax | A PSA/IL-2/GM-CSF encoding vaccine | I | N/A | NCT02058680 | |
| | 22 | DRibble | Tumor-derived autophagosome-based vaccine | I | N/A | NCT02234921 | |
| | 23 | Ad-sig-hMUC-1/eccdCD40L | Adenovirus-based vaccine encoding MUC-1/CD40L fusion | I | N/A | NCT02140996 | |
| | 24 | PrCa VBIR | Heterologous prime/boost vaccination platform | I | N/A | NCT02616185 | |
| | 25 | GVAX-PCa | Irradiated PC3 and LNCaP cell line with GM-CSF | Discontinued as monotherapy (combinations still being explored) | IR elicited<br>Few SAE<br>No Δ in OS | NCT01696877 | 20,21 |
| Autologous Cell Infusion | 26 | CryoIT DC | Autologous dendritic cells administered to cryoablated tumor region | I | N/A | NCT02423928 | |
| | 27 | Autologous NKT cells | Autologous natural killer T cell isolation, expansion, and reinfusion | I | N/A | NCT01801852 | |
| | 28 | Autologous NK cells | Autologous natural killer cell isolation, expansion, and reinfusion | I | N/A | NCT00720785 | |
| CAR-T | 29 | CAR+ T cells/PSMA | Autologous T cells engineered to express a chimeric antigen receptor (CAR) specific for PSMA | I | N/A | NCT01140373 | |
| Bispecific T cell engager | 30 | BAY2010112 | Bispecific T cell engager (BiTE) specific for CD3 and PSMA | I | N/A | NCT01723475 | |
| | 31 | MOR209/ES414 | Bispecific T cell engager (BiTE) specific for CD3 and PSMA | I | N/A | NCT02262910 | |
| | 32 | MT110 | Bispecific T cell engager (BiTE) specific for CD3 and EpCAM | I | N/A | NCT00635596 | |
| Checkpoint Antibody | 33 | Pembrolizumab | Monoclonal antibody blocking PD-1 ligation by PD-L1 and PD-L2 | II | No OR<br>Some SAE | NCT02312557 (and many combinations) | 43 |
| | 34 | Ipilimumab | Monoclonal antibody blocking CTLA-4 ligation by CD80 or CD86 | Previous Phase III. Still under testing as | Δ in PSA levels<br>Some SAE | NCT02279862 (and many | 40,41 |

| | # | Drug Name | Description | Current Phase | Results | Ongoing Trials | References |
|---|---|---|---|---|---|---|---|
| | | | | monotherapy and in combination | No Δ in OS | combinations) | |
| | 35 | Tremelimumab | Monoclonal antibody blocking CTLA-4 ligation by CD80 or CD86 | Discontinued as monotherapy (combinations still being explored) | Δ in PSA DT<br>Some SAE | NCT02616185<br>NCT02643303 | 67 |
| | 36 | Nivolumab | Monoclonal antibody blocking PD-1 ligation by PD-L1 and PD-L2 | Discontinued as monotherapy (combinations still being explored) | No OR[a]<br>Few SAE | NCT02601014 | 42 |
| Microenvironment Disruption | 37 | LY3022855 | Monoclonal antibody specific for CSF1R, depletes tumor-associated macrophages | I | N/A | NCT02265536 | |
| | 38 | Sunitinib | Tyrosine kinase inhibitor that depletes MDSCs and inhibits tumor angiogenesis | Discontinued as monotherapy (combinations still being explored) | Δ in PFS[a]<br>Common SAE<br>No Δ in OS | NCT01803503<br>NCT00329043 | 45 – 47 |
| | 39 | Tasquinimod | Engages with S100A9 and depletes MDSCs and inhibits tumor angiogenesis | Discontinued as monotherapy (combinations still being explored) | Δ in PFS<br>Common SAE<br>No Δ in OS | NCT01513733<br>NCT02159950 | 51 |

[a] Δ = Change. SAE = Serious Adverse Event. SD = Stable Disease. IR = Immune Response. OS = Overall Survival. DT = Doubling Time. OR = Objective Response. PFS = Progression-Free Survival.

[b] "No SAE" = 0 patients, "Few SAE" = 1-10% of patients, "Some SAE" = 10-25%, "Common SAE" = 25+%